UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

for Acct

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

June 28, 2011

MEMORANDUM

Subject: Acute Toxicity Review for EPA Reg. No. 1043-REA
DP Barcode: D388063

From: Chris Jiang, Chemist
Chemistry and Toxicology Team
Product Science Branch
Antimicrobials Division (7510P)

Chris Jiang
6/28/11

Through: Karen Hicks, Team Leader
Chemistry and Toxicology Team
Product Science Branch
Antimicrobials Division (7510P)

To: Velma Noble PM 31\Cletis Mixon
Regulatory Management Branch I
Antimicrobials Division (7510P)

Applicant: Steris Corporation

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Didecyl dimethyl ammonium chloride	10.0 %
Other Ingredient(s):	90.0 %
Total:	100.0 %

BACKGROUND: The registrant has submitted an acute toxicity package for the registration of this disinfectant. The package includes a label, a Confidential Statement of Formula, an acute oral toxicity study (MRID 48412614), an acute dermal toxicity study (MRID 48412615), an acute inhalation study (MRID 48412616), a dermal sensitization study (MRID 48412617), and a summary of acute toxicity characteristics (MRID 48412618). The contractor has conducted a primary review of this submission and Product Science Branch of Antimicrobials Division has conducted a secondary review, which supersedes the primary review.

RECOMMENDATIONS:

1. The studies for acute oral toxicity, acute dermal toxicity, and dermal sensitization are acceptable.

2. The waivers for eye irritation and dermal irritation are acceptable. Because the test material has a high pH, the registrant is placing the test material in toxicity category I.

3. The study for acute inhalation is **acceptable**; however, this reviewer is placing the test material in toxicity category II when the laboratory report placed the test material in toxicity category III. Because the test material was corrosive, the laboratory believed that the only way to conduct an acute inhalation study was to dilute the product. No deaths occurred in the study, gross necropsies were unremarkable, and the study results showed that the LC_{50} was on the border between toxicity category II and toxicity category III.

4. The historical positive control for sensitization was older than six months prior to the start of the test for the test compound so the laboratory emailed this reviewer a more recent positive control study.

5. The acute toxicity profile for 1043-REA is currently:

Study	MRID Number	Toxicity Category	Study Status
Acute Oral Toxicity	48412614	III	Acceptable
Acute Dermal Toxicity	48412615	IV	Acceptable
Acute Inhalation Toxicity	48412616	II	Acceptable
Primary Eye Irritation		I	Waiver
Primary Skin Irritation		I	Waiver
Dermal Sensitization	48412617	Nonsensitizer	Acceptable

LABELING

1. The signal word is **DANGER**.

2. The precautionary labeling must read, "**Corrosive**. Causes irreversible eye damage and skin burns. Do not get in eyes, on skin, or on clothing. May be fatal if inhaled. Harmful if swallowed. Do not breathe vapor or spray mist. Wear coveralls worn over long-sleeved shirt and long pants, socks, chemical-resistant footwear, and natural rubber gloves. Wear goggles, face shield, or shielded safety glasses. Wear a respirator with an organic-vapor removing cartridge with a prefilter approved for pesticide (MSHA/NIOSH approval number prefix TC-23C), or a canister approved for pesticides (MSHA/NIOSH approval number prefix

TC-14G) or a NIOSH approved respirator with an organic vapor (OV) cartridge or canister with any N, R, P, or HE prefilter. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Remove and wash contaminated clothing before reuse.

3. The current first aid statements must read:

If in eyes:
-Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing.

If on skin or clothing:
-Take off contaminated clothing.
-Rinse skin immediately with plenty of water for 15-20 minutes.
-Call a poison control center or doctor for treatment advice.
-Call a poison control center or doctor for treatment advice.

If inhaled:
-Move person to fresh air.
-If person is not breathing, call 911 or an ambulance, then give artificial respiration, preferably mouth-to-mouth if possible.

If swallowed:
-Call a poison control center or doctor immediately for treatment advice.
-Have a person sip a glass of water if able to swallow.
-Do not induce vomiting unless told to by a poison control center or doctor
-Do not give anything by mouth to an unconscious person.

4. "**Note to Physician**: Probable mucosal damage may contraindicate the use of gastric lavage." must appear on the label.

5. This product meets the criteria to be labeled as a Restricted-Use Pesticide based on the waivers for skin irritation and eye irritation. If regulatory does not want the product to be labeled as a Restricted-Use Pesticide, then this product must be packaged in CRP (Child-Resistant Packaging).

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (81-1, 870.1100)

Product Manager: Velma Noble
MRID No.: 48412614

Reviewer: Chris Jiang
Study Completion Date: Sept. 20, 2010
Report No.: 29936

Testing Laboratory: Eurofins PSL
Author: Jennifer Durando

Quality Assurance (40 CFR 160.12): A statement of GLP compliance was included.

Test Material: EXP 10006, lot 6781-52, clear colorless to slight yellow liquid
Dosage: 175 mg/kg, 550 mg/kg, 1750 mg/kg

Species: Female derived albino Sprague-Dawley rats
Age: Eight to twelve weeks
Weight: 163 to 214 grams at experimental start
Source: Ace Animals, Inc., Boyertown, PA

Conclusions:

1. **LD_{50} (mg/kg):** LD_{50} = 1030 mg/kg
2. **The estimated LD_{50} is equal to 1030 mg/kg.**
3. **Toxicity Category**: III **Classification**: Acceptable

Procedure (Deviations from 81-1): The Up-and-Down Procedure was used. Females were used because they are more sensitive than males. The original study director left the company so the study was reassigned. The relative humidity was outside of the range specified in the protocol. These changes had no impact on the integrity of the study.

Results:

Reported Mortality

Animal Number	Dosage (mg/kg)	Short-Term Outcome	Long-Term Outcome
3101	5000	X	X
3102	175	O	O
3103	550	O	O
3104	1750	X	X
3105	550	O	O
3106	1750	X	X
3107*	550	-	-
3108	550	O	O
3109	1750	X	X

O = lived, **X** = died
*Animal 3107 was removed from dose progression due to injury and was replaced by animal 3108.

Observations:
Animal 3101 was tested at a dose of 5,000 mg/kg. Because the animal died, the Up-and-Down procedure was initiated.

175 mg/kg: The animal appeared normal and healthy throughout the study.

550 mg/kg: Clinical signs included ano-genital staining, diarrhea, and reduced fecal volume.

1750 mg/kg: All animals died within one day of test substance administration. No toxic signs were observed prior to death.

5000 mg/kg: Clinical signs included hypoactivity, hunched posture, piloerection, and reduced fecal volume.

Gross Necropsy Findings:
175 mg/kg: Gross necropsy was unremarkable.

550 mg/kg: Gross necropsies were unremarkable.

1750 mg/kg: Gross necropsies revealed moderately red lungs and intestines and distended stomach and intestines.

5000 mg/kg: Gross necropsy revealed discoloration of the intestines. It also showed a portion of the intestines that was distended.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (81-2, 870.1200)

Product Manager: Velma Noble
MRID No.: 48412615

Reviewer: Chris Jiang
Study Completion Date: Sept. 20, 2010
Report No.: 29937

Testing Laboratory: Eurofins PSL
Author: Jennifer Durando

Quality Assurance (40 CFR 160.12): A statement of GLP compliance was included.

Test Material: EXP 10006, lot 6781-52, clear colorless to slight yellow liquid
Dosage: 5000 mg/kg

Species: Five male and five female derived albino Sprague-Dawley rats
Age: Nine to ten weeks
Weight: ♂: 292 to 334 grams at experimental start; ♀: 203 to 232 at experimental start
Source: Ace Animals, Inc., Boyertown, PA

Conclusions:

1. **LD_{50} (mg/kg):** **Males** > 5000 mg/kg
   Females > 5000 mg/kg
   Combined > 5000 mg/kg
2. **The estimated LD_{50} is greater than 5000 mg/kg**.
3. **Toxicity Category**: IV **Classification**: Acceptable

Procedure (Deviations from 81-2): The clinical observations for days 4 and 5 were inadvertently not performed. The original study director left the company so the study was reassigned. These changes had no impact on the integrity of the study.

Results:

Reported Mortality

Dosage (mg/kg)	(Number Deaths/Number Tested)		
	Males	Females	Combined
5000	0/5	0/5	0/10

Observations: Clinical signs included corrosion, eschar, discoloration, and blanching at the dose site.

Gross Necropsy Findings: Gross necropsies were unremarkable.

DATA REVIEW FOR ACUTE INHALATION TOXICITY (§81-3, 870.1300)

Product Manager: Velma Noble
MRID No.: 48412616

Reviewer: Chris Jiang
Study Completion Date: Oct. 31, 2010
Report No.: 29938

Testing Laboratory: Eurofins PSL
Author: Jennifer Durando

Quality Assurance (40 CFR 160.12): A statement of GLP compliance was included.

Test Material: EXP 10006, lot 6781-52, clear colorless to slight yellow liquid
Dosage: 0.056 mg/L
(Nominal: 0.744 mg/L) (Gravimetric: 0.056 mg/L)
0.518 mg/L
(Nominal: 1.732 mg/L) (Gravimetric: 0.518 mg/L)

Species: Two groups each of five male and five female derived albino Sprague-Dawley rats
Age: Eight to ten weeks
Weight: ♂: 252 to 343 grams at experimental start; ♀: 183 to 240 grams at experimental start
Source: Ace Animals, Inc., Boyertown, PA

Summary:

1. **LC_{50} (mg/L)** : > 0.518 mg/L
2. **The LC_{50} is greater than 0.518 mg/L.**
3. **MMAD**: 2.35 µm
4. **Toxicity Category**: II **Classification**: Acceptable

Procedure (Deviations from 81-3): The relative humidity was outside of the range specified in the protocol. The original study director left the company so the study was reassigned. These changes had no impact on the integrity of the study.

Results:

Reported Mortality

Exposure Concentration (mg/L)	Number Dead / Number Tested		
	Males	Females	Combined
0.056	0 / 5	0 / 5	0 / 10
0.518	0 / 5	0 / 5	0 / 10

Chamber Atmosphere

Exp. Conc. (mg/L)	Sample	MMAD (µm)	GSD (µm)	Cumulative % of Particles < Effective Cutoff Diameter (µm)[1]								
				0.0	0.4	0.7	1.1	2.1	3.3	4.7	5.8	9.0
0.056	1	2.3	1.89	0.0	1.0	4.7	12.5	36.5	70.8	87.5	93.2	97.9
	2	2.4	1.82	0.0	0.5	3.5	10.4	34.7	69.8	87.6	93.6	98.5
0.518	1	2.3	1.94	0.0	0.7	3.7	10.7	37.0	71.0	90.7	94.0	98.0
	2	2.4	2.00	0.0	0.0	3.4	10.8	34.1	66.8	86.9	92.6	97.7

[1]Percent of particles smaller than corresponding effective cutoff diameter

Chamber Environment During Exposure

Chamber Volume (L)	6.7
Average Total Airflow Volume (Lpm)	25.7
Air Changes Per Hour	230
Mean Temperature (°C)	20 to 23
Mean Relative Humidity (%)	67 to 77

Clinical Observations:

0.056 mg/L: All animals were active and healthy throughout the study.

0.518 mg/L: Clinical signs included irregular respiration, hypoactivity, and dry to moist rales.

Gross Necropsy Findings:

0.056 mg/L: Gross necropsies were unremarkable.

0.518 mg/L: Gross necropsies were unremarkable.

DATA REVIEW FOR DERMAL SENSITIZATION TESTING (81-6, 870.2600)

Product Manager: Velma Noble
MRID No.: 48412617

Reviewer: Chris Jiang
Study Completion Date: Sept. 20, 2010
Report No.: 29939

Testing Laboratory: Eurofins PSL
Author: Jennifer Durando

Quality Assurance (40 CFR 160.12): A statement of GLP compliance was included.

Test Material: EXP 10006, lot 6781-52, clear colorless to slight yellow liquid
Positive Control: α-Hexylcinnamaldehyde (HCA)

Species: Male Hartley guinea pig
Weight: ♂: 319 to 381 at experimental start
Age: Young adult
Source: Elm Hill Breeding Laboratories, Chelmsford, MA

Method: Magnusson and Kligman Guinea Pig Maximization Test

Summary:

1. **This Product is not a dermal sensitizer.**
2. **Classification**: Acceptable

Procedure (Deviation From §81-6): Relative humidity was outside of the range specified in the protocol. The original study director left the company so the study was reassigned. These deviations had no impact on the integrity of the study.

Procedure:
After preliminary testing, the main test was undertaken.

Induction Phase:
Intradermal Injection: On the first day of the induction period, the test animals received six intradermal injections (0.1 mL each) in the shaved suprascapular area as follows. The preparations were thoroughly mixed prior to application with a homogenizer.

Injection Site No.		Material Injected
Left Upper Back	Right Upper Back	
1	2	Emulsion of Freund's Adjuvant Complete (50% v/v in distilled water)
3	4	1% w/w mixture of test substance in distilled water
5	6	1% w/w mixture of test substance in an emulsion of Freund's Adjuvant Complete (50% v/v in distilled water)

Topical Application: Seven days after the intradermal injections, the topical induction phase was conducted. The suprascapular area over the injection sites was re-clipped free of fur. Twenty-four hours prior to topical induction, the dose area of each test and sham control animal was pre-treated with 5% w/w sodium lauryl sulfate (SLS) mixture in petrolatum in order to enhance the potential for sensitization by provoking a mild inflammatory reaction. The site remained uncovered until the topical induction patch was applied. Prior to the topical induction, the sites were cleansed of any residual SLS and dose sites were re-clipped. Approximately twenty-five hours after SLS application, readings were made of local reactions (erythema) according to the scoring system. Five tenths of a milliliter of a 0.75% w/w mixture of the test substance in distilled water was applied to the dose site and covered with a 2 cm x 4 cm, 2-ply gauze patch. The patch was covered with plastic wrap and secured in place with non-allergenic Durapore adhesive tape to avoid dislocation of the patch and to minimize loss of the test substance. After the 48-hour exposure period, the patches were removed and the test sites were cleaned of residual test substance. Approximately one hour after patch removal, readings were made of local reactions (erythema) according to the scoring system. The sham control group received the same treatment using distilled water.

Challenge Phase: Prior to challenge, a naïve site on the right side of each test and sham control animal was clipped free of fur. Twenty-two days after test initiation, four-tenths of a milliliter of a 0.25% w/w mixture of the test substance in distilled water (HNIC) was applied to a naïve site on each test animal using an occlusive 25 mm Hill Top Chamber. The chambers were secured in place and wrapped with non-allergenic Durapore adhesive tape to avoid dislocation of the chambers and to prevent evaporation. After the 24-hour exposure period, the chambers were removed and the sites were cleaned of residual test substance. Approximately 24 and 48 hours after patch removal, these sites were evaluated for a sensitization response (erythema) according to the scoring system.

Results:

Topical Induction Phase:

Test Animals (0.75% w/w mixture of the test substance in distilled water): Faint to moderate erythema (1-2) was noted at all test sites one hour after patch removal.

Challenge Phase:

Test Animals (0.25% w/w mixture of the test substance in distilled water): Very faint erythema (0.5) was noted for ten of twenty test sites 24 hours after challenge patch removal. Irritation persisted at three of these sites through 48 hours.

The historical positive control showed appropriate results.

Test Animal Group Skin Reaction Scores

Treatment Phase	Induction		Challenge	
Concentration	0.75%[1]	0.75%[1]	0.25%[2]	
Hours	Pre-Induction Score[3]	Skin Irritation Score[4]	24 Hours after challenge	48 Hours after challenge
Animal No. / Sex				
Test Group				
3601 / M	2	2	0	0
3602 / M	2	1	0	0
3603 / M	2	2	0.5	0
3604 / M	2	2	0.5	0
3605 / M	2	2	0.5	0
3606 / M	2	2	0	0
3607 / M	2	2	0.5	0.5
3608 / M	2	1	0.5	0
3609 / M	2	2	0.5	0
3610 / M	2	2	0.5	0
3611 / M	2	2	0	0
3612 / M	2	1	0.5	0.5
3613 / M	2	1	0.5	0
3614 / M	2	2	0	0
3615 / M	2	1	0	0
3616 / M	2	2	0	0
3617 / M	2	2	0.5	0.5
3618 / M	2	1	0	0
3619 / M	2	1	0	0
3620 / M	2	2	0	0

[1]Five-tenths of a milliliter of a 0.75% w/w mixture of the test substance in distilled water was applied.
[2]Four-tenths of a milliliter of a 0.25% w/w mixture of the test substance in distilled water was applied.
[3]25 hours after sodium lauryl sulfate application
[4]One hour after patch removal